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Safety of newer generation anti-epileptic drugs in non-accidental overdose: an Irish population study

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Summary Seven new anti-epileptic drugs (AEDs) have become available in Ireland over the last 10 years; data from animal models and clinical trials suggest that they have a superior safety profile to older AEDs. A specific relationship between epilepsy and psychiatric co-morbidity has long been recognised, including the relationship between epilepsy and suicide.

AEDs are common agents taken in intentional drug overdoses.

We undertook a study to review the frequency and outcome of non-accidental overdose with seven new AEDS in an Irish population from 1996 to 2000. *Method*: All reported cases of drug overdoses with AEDs from 1996 to 2000 were reviewed. Data was provided by the National Poisons Information Centre, Beaumont Hospital and the Central Statistics Office. Medical records from Beaumont Hospital were reviewed in specific cases of serious drug toxicities. An extensive review of published literature reviewing the safety profile of these AEDs was performed and medical literature retrieved from the databases of the pharmaceutical industry was similarly reviewed. *Results*: Of the 164 reported cases of newer AEDs, there were no fatalities among the cases followed up. *Conclusion*: The absence of mortalities and serious consequences from deliberate self-poisoning with the newer agents is supportive evidence for the superior safety profile of the newer AEDs.

Introduction

Over the last 10 years, seven new anti-epileptic drugs (AEDs) have become available in Ireland. These newer agents have a number of advantages over older AEDs.[1] Many have longer half lives, enabling once or twice daily dosing. They have a reduced potential for drug interactions, and although most of them undergo extensive hepatic metabolism (with the exception of levetiracetam, gabapentin and vigabatrin), they are less likely to cause hepatic enzyme induction, facilitating their use as add-on agents and making polypharmacy safer.[2,3] Data from animal models and clinical trials suggest that they have a safety profile which is superior to the older AEDs.

There are estimated to be up to 40,000 people with epilepsy in Ireland, affecting 1 in 200 adults and 1 in 100 children. This is comparable to the prevalence figures world-wide, estimated at 5—10 per 1000.[4] Epilepsy carries with it a mortality rate

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which is two to three times that of the general population.[5,6] While this excess is made up partly by seizure-related accidental deaths[7] (trauma, drowning), sudden unexpected deaths in epilepsy[8] (SUDEP) and death from underlying diseases (e.g. strokes, infections of the central nervous system), a recognised contribution comes from drug intoxication.[9–11]

Gowers in 1901 was the first to recognise and document a specific association between epilepsy and suicide.[12] The association between epilepsy and psychiatric co-morbidity is well recognised. AEDs are relatively common agents taken in intentional drug overdose.[13] Hawton et al.[14] looked at the association between suicide and epilepsy over a 2-year period (1976–1977). Eighty-four percent of suicide attempts among patients with epilepsy in this study involved self-poisoning, and in 65% of these cases, AEDs were consumed. A 6-year retrospective study by Manon-Espaillat et al.[15] found that suicide occurred in 18% of reported drug intoxications with AEDs between 1979 and 1985. The incidence of suicide in patients with epilepsy as a percentage of deaths in the same population was averaged over 17 studies at 13.2%. More recent figures suggest an incidence of 5–7%[16] and male patients with epilepsy are a particularly vulnerable group.[17] The prevalence of depression has been reported as 60% in certain epilepsy populations.[18,19] Mendez et al.[20] reviewed the possible causative factors for deliberate self-poisoning in epilepsy. Across the cohort of patients who were hospitalised for suicide attempts by drug overdose, when matched by age, sex and race, patients with epilepsy had more borderline personality disorders with multiple impulsive suicide attempts and psychosis compared with patients without epilepsy.[21] Patients with complex partial seizures were especially felt to be at high risk from attempted suicide. A case control study evaluating a large cohort of patients in Sweden, found a high incidence of psychiatric disease amongst the patients with epilepsy who attempted suicide, with depression being the most common diagnosis.[22,23] In excess of 81% of this group carried a diagnosis of intercurrent psychiatric disease. Hence, the safety of anti-convulsants has significant implications for the management and prevention of mortality in situations of non-accidental overdose.

In acute toxicity studies with gabapentin in mice and rats, at maximum doses of 2000–8000 mg/kg, ataxia and laboured breathing were reported but no deaths. With gabapentin, at doses exceeding 600 mg, saturation of the carrier-mediated absorption pathway results in reduced bioavailability with increasing doses.[24] The mean lethal doses of lamotrigine in mice and rats have been established.[25] Acute median oral lethal doses for mice were 202–245 and 163–205 mg/kg for rats. Animal studies with levetiracetam demonstrated selective protection against induced seizures with a very high safety margin for the drug in rodents.[26] With oxcarbazepine, there is a low level of hepatic induction of cytochrome P450 microsomal system.[27]

In acute toxicity studies across multiple species, extremely high doses of oral oxcarbazepine were tolerated and there were no compound-related deaths. Animal studies with topiramate demonstrated, there was no accumulation of the drug at higher doses and there was no autoinduction or inhibition of enzymes that metabolise topiramate.[28] The clinical development of vigabatrin was delayed by the finding of microvacuolation in the white matter of rodents and dogs.[29] Since then however, extensive studies have confirmed that microvacuolation is species specific and does not occur in humans.

Methods

We undertook a study to examine the frequency and outcome of non-accidental overdose with seven newer AEDs in an Irish population during the 5-year period 1996–2000. A study of this nature has not been undertaken in Ireland previously. This retrospective study was performed in the Department of Neurology, Beaumont Hospital in collaboration with the National Poisons Information Centre (NPIC), Beaumont Hospital.

We reviewed data provided by the NPIC and the Central Statistics Office (CSO). The NPIC are contacted by hospitals all around the country when patients present to Accident and Emergency (A&E) departments with deliberate self-poisoning. The type of agent(s) and severity of the overdose reported is noted by the NPIC and any potentially fatal overdoses are followed up by the NPIC through telephone contact with the relevant medical team in Beaumont Hospital. The CSO keep a register of all reported deaths due to AEDs. Deaths from anti-convulsant agents other than phenytoin and succinimides are represented within a single category by the CSO, therefore it is not possible to distinguish mortalities from data between individual AEDs.

In addition, we undertook an extensive literature review of established case reports of overdose with the newer AEDs and the published literature reviewing the general safety profile of these drugs. We were assisted by medical information from

the pharmaceutical industry retrieved from their databases, specifically addressing the safety profile of these agents in situations of overdose. The pharmaceutical industry had comprehensive data for any potential fatalities from poisoning with the newer AEDs from 1996 to 2000.

A comparative review was undertaken with the older agents for the same time period.

Results

The total number of reported overdoses using any of the seven newer AEDs over the 5-year period 1996—2000 inclusive was 164. In addition there were three reports from the United Kingdom and seven others requesting information.

The majority of overdoses involved more than one agent (115 of 164 cases). There were no reported mortalities among the cases reported from 1996 to 2000 (see Table 1). It was possible to confirm this through follow up information from both the NPIC and the pharmaceutical industry data.

From 1996 to 2000, eight of the cases of deliberate self-poisoning recorded above were admitted and treated at Beaumont Hospital. Three patients overdosed with lamotrigine, three patients with gabapentin and two patients with vigabatrin. Representative brief case histories of their brief admissions are as follows.

Case 1

An 18-year-old girl, with a background of epilepsy, presented to the A&E department with convulsions. Through collateral history, it was discovered that she has ingested 45 tablets of lamotrigine and 20 tablets of penicillin in the previous 2 h. The precise doses ingested are not known. She was treated with activated charcoal and underwent cardiac monitoring. She recovered on supportive therapy without complication.

Case 2

A 21-year-old man presented to the A&E department with drowsiness having taken an overdose of his medications which consisted of sodium valproate, carbamazepine, thioridazine and gabapentin. It was uncertain how many tablets he

Table 1 Figures for non-accidental cases of overdose with the newer AEDs based on reports to the NPIC, Beaumont Hospital.

Drug	Year	No. of reports	Single/multiple
Gabapentin	1996	2	Both > 1 drug
	1997	1	>1 drug
	1998	11	7 cases > 1 drug
	1999	7	4 cases > 1 drug
	2000	12	10 cases > 1 drug
Lamotrigine	1996	8	6 cases > 1 drug
	1997	18	11 cases > 1 drug
	1998	17	13 cases > 1 drug
	1999	28	17 cases > 1 drug
	2000	26	16 cases > 1 drug
Levetiracetam	1996—1999	0	
	2000	1	>1 drug
Oxcarbazepine	1996—2000	0	
Tiagabine	1996—1998	0	
	1999	2	>1 drug
	2000	3	>1 drug
Topiramate	1996—1998	0	
	1999	1	>1 drug
	2000	6	4 cases > 1 drug
Vigabatrin	1996	6	3 cases > 1 drug
	1997	3	All > drug
	1998	6	5 cases > 1 drug
	1999	3	All > 1 drug
	2000	3	All > 1 drug

ingested in total. He was too drowsy for gastric lavage or charcoal administration. He was monitored closely and treated symptomatically and subsequently made a complete recovery.

Case 3

A 22-year-old woman with a background history of epilepsy, presented to the A&E department, admitting to consuming unknown quantities of vigabatrin and carbamazepine. She was asymptomatic at presentation and was treated with activated charcoal. She remained asymptomatic and was discharged after overnight observation and psychiatric review.

Table 3 Total number of anti-convulsant overdoses involving older agents reported to the NPIC between 1996 and 2000, excluding any cases involving the seven newer anti-convulsants.

Name of drug	Number of reports to NPIC 1996—2000	Number of cases with >1 drug involved
Carbamazepine	149	87
Clobazam	10	7
Ethosuximide	0	0
Phenobarbitone	35	16
Phenytoin	43	27
Sodium valproate	83	54

Discussion

From review of published literature and medical information provided from the pharmaceutical industry database, deliberate overdoses with the seven newer agents are infrequent (see Table 2). Acute life-threatening toxicity has not been observed to date with gabapentin. Reduced absorption of the drug at higher doses may limit drug bioavailability at the time of overdosing, therefore reducing toxicity. Overdose with up to 49 g of gabapentin has resulted in no serious consequences.[24] With lamotrigine, numerous case reports show recovery without serious sequel for doses up to 4.5 g.[30—32] However, fatalities have been reported in cases of lamotrigine poisoning. In a post-mortem case, where the distribution of lamotrigine was determined, the blood concentration of lamotrigine was 52 mg/l (therapeutic range of up to 14 mg/l) with no other AEDs detected. The precise cause of death in this case was undetermined.[33] Both gabapentin and lamotrigine confer an additional advantage in prescribing that they have both been reported to have mood stabilising effects in patients.

There have been no case reports relating to acute intoxication with either levetiracetam or oxcarbazepine to date. There have been unpublished reports of overdoses with topiramate, with overdoses of up to 100 g of topiramate, without any resulting fatality. A study reviewing 23 cases of overdose with tiagabine reported complete recovery in all patients.[34,35] There have been no case reports relating to acute intoxication with either levetiracetam or oxcarbazepine and no reported fatalities with vigabatrin in the published literature to date.

In our study, we found that despite the number of patients who took overdoses of the newer AEDs, whether in isolation or in combination with other drugs, there were no fatalities seen amongst the 164 reported cases. The only other comparable population study in the literature was a Polish study, which was conducted between 1990 and 1992 by Miller et al., looking at suicide attempts reported through their Poisons Control Centre.[36] In the above

Table 2 Case reports retrieved from pharmaceutical industry databases based on information submitted to the AED manufacturers.

Drug	Pharmaceutical industry data
Gabapentin	Unpublished case reports submitted to manufacturer. Single published case report of ingestion of 49 g with complete recovery following supportive treatment.[24]
Lamotrigine	Overdoses up to 15 g have been reported. Numerous case reports published and unpublished available. Fatalities reported from CNS and cardiovascular toxicity.
Levetiracetam	No case reports.
Oxcarbazepine	No case reports.
Tiagabine	Numerous case reports including 23 cases published in a single study.[35] No serious sequel reported.
Topiramate	Five cases of overdoses with doses ranging from 1.8 to 100 g. One unpublished case report submitted to the manufacturer. All cases recovered without complication.
Vigabatrin	Single published case report of overdosage.

Table 4 Number of overdoses with older AEDs admitted to Beaumont Hospital from 1996 to 2000.

Year	Number of overdoses with older AEDs admitted to Beaumont Hospital	Outcome of admissions
1996	1	Overnight admission.
1997	3	No fatalities. One overnight admission. Two cases requiring hospitalisation for >1 week and prolonged monitoring.
1998	3	No fatalities. One prolonged admission (>1 week).
1999	12	No fatalities. One prolonged admission (1 week).
2000	7	No fatalities. One prolonged admission (>1 week).

study, 9% of all patients treated for attempted suicide carried a diagnosis of epilepsy.

The number of cases of non-accidental overdose with the older anti-convulsants reported to the NPIC between 1996 and 2000 is represented in Table 3. The outcome of cases that were admitted solely to Beaumont Hospital is represented in Table 4. There were no fatalities amongst the 26 cases admitted. Five of these admissions, however were prolonged hospital admissions lasting a minimum of 1 week, signifying more serious consequences from drug toxicity.

There were 320 cases of poisoning with older AEDs reported to the NPIC. The number of fatalities outside admissions to Beaumont Hospital cannot be determined for the same time period. There are, however, numerous case reports citing non-accidental overdoses and case reports of fatalities with most of the older AEDs.[37–39] Acute, life threatening fatalities have been reported with phenobarbitone,[37] sodium valproate,[38] phenytoin[39] and carbamazepine.[40] This contrasts with the paucity of fatalities from the newer AEDs.

Given the high incidence of impulsive suicidal gestures reported among patients with epilepsy, especially partial epilepsy, as well as the high prevalence of depression, the newer generation AEDs may confer an additional advantage in prescribing. The absence of serious consequences from deliberate self-poisoning of these agents in our study is supportive evidence for their superior safety profile in normal prescribing but also in the management and prevention of fatality from the significant risk of non-accidental overdose of AEDs in individuals with epilepsy.

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